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Multicentric Castleman's Disease With an Increased Serum Level of Macrophage Colony-Stimulating Factor

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We describe a 74-year-old patient with multicentric Castleman's disease (MCD) whose serum macrophage colony-stimulating factor level was elevated. Serum levels of tumor necrosis factor-α and interleukin 6 were also elevated at presentation, and they returned to normal levels after chemotherapy. Although the total serum cholesterol level was below normal on admission, it increased after chemotherapy. These results suggest that the activation of monocytes or macrophages may be involved in certain pathological phenomena in MCD. Am. J. Hematol. 54: 321–323, 1997.

Key words: multicentric Castleman's disease; M-CSF

INTRODUCTION

Giant lymph-node hyperplasia, the so-called Castleman's disease (CD), was first described in 1956 as a relatively rare benign disease, and it appears most frequently as a solitary mass in the mediastinum [1]. Histologically, CD was classified into two variants: the hyaline-vascular type, which accounts for >90% of CD, showing hyaline-vascular follicles and interfollicular capillary proliferation, and the plasma-cell type, which accounts for <10%, characterized by hyperplasia of follicles with intervening sheets of plasma cells [2,3]. Multicentric Castleman's disease (MCD), histologically resembling CD plasma-cell type, has systemic manifestations consisting of systemic lymph-node swelling, fever, anemia, polyclonal or monoclonal hypergammaglobulinemia, positivity for autoantibodies, and an increase of acute-phase proteins [4,5]. Recently, it was reported that interleukin-6 (IL-6) plays a central role in CD [6,7] and MCD [8], which provided the clue in elucidating the pathophysiology of MCD as probably arising from disregulated immune responses.

In this report, we present an MCD patient whose serum cytokine concentrations were followed up, and we discuss the patient's clinicopathological relevance.

CASE REPORT

A 74-year-old Japanese woman was admitted to the Akita Labor Injury Hospital on February 16, 1994, because of systemic lymphadenopathy and dyspnea. The patient had been well until a month earlier, when she noticed left cervical lymphadenopathy and experienced insidious onset of fatigue. Two weeks before admission she began to have intermittent low-grade fever and mild exertional dyspnea. The dyspnea worsened, and systemic lymphadenopathy developed during the last 2 weeks before admission. She had lost 4.0 kg during her illness. She neither smoked nor drank. There was no history of exposure to animals, chemicals, or industrial dust. On physical examination, the patient was thin and dyspneic and appeared severely ill. Her vital signs were normal. No rash or pustules were seen. Her temperature was 38.2°C, pulse rate was 100/min, and respirations were 28/min. Her blood pressure was 162/80 mm Hg. Bilateral cervical, axillary, and inguinal lymph nodes, which were

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firm, nontender, mobile, and nonfluctuant, and 0.5–2.0 cm in size, were palpated. There were diminished breath sounds bilaterally with wheezing. The heart was normal; no murmur was heard. The liver and spleen were not felt. The extremities were normal. Room-air arterial blood gas indicated pH 7.38, pCO_2 41.0 mm Hg, pO_2 52 mm Hg, HCO_3 22.0 mmol, and O_2 sat 92%. Pulmonary function studies showed VC of 55.3% and FEV 1.0% of 92.8%, suggesting restrictive ventilatory disorders. Radiographs of the chest revealed bilateral hilar swelling. A computed tomographic (CT) scan of the thorax disclosed bilateral hilar lymphadenopathy and a huge tumor at the mediastinum. Interstitial shadows were observed in both lower lung fields. The laboratory examination showed that the hemoglobin was 11.2 g/100 ml, the leukocyte count 6.9 $\times 10^9$/l with 31% eosinophils, and the platelet count 196 $\times 10^9$/l. The erythrocyte sedimentation rate was 122 mm/hr, serum iron was 760 μg/l, CRP was 2.36 mg/100 ml, anti-nuclear antibodies were 1:320 (homogenous type), and serum C3, C4, and CH_{50} were 57 mg/100 ml, 9.3 mg/100 ml, and 28 U/mg/100 ml, respectively. Total protein was 8.28 g/100 ml with polyclonal 34% gammaglobulin on electrophoresis. Quantitative determinations of gamma-globulins of IgG, A, and M were 3,397, 1,357, and 126 mg/100 ml, respectively. Serum and urinary immunoelectrophoresis showed no abnormal proteins. Tests for Bence Jones protein were negative. Direct Coombs' test was positive. Bone-marrow aspirate contained 11.0% plasma cells of normal appearance with an increased number (250/μl) of megakaryocytes. The following data were within normal limits or negative: serum calcium, phosphate, sodium, potassium, chloride, BUN, creatinine, uric acid, GOT, GPT, LDH, alkaline phosphatase, bilirubin, glucose, HBsAg, HBsAb, HCV antibody, TPHA, HTLV, HIV, and cold agglutination test.

Biopsies were performed from the right cervical lymph node before chemotherapy. Examination of the lymph nodes showed the presence of large hyperplastic follicles and interfollicular capillary proliferation accompanied by intervening sheets of plasma cells in the interfollicular region, consistent with Castleman's disease, plasma-cell type. With immunostaining for cytoplasmic immunoglobulins, most of the interfollicular plasma cells had kappa chains, with a minority positive for lambda chains. Plasma cells, scattered in the interfollicular area, were positive for IgG, IgA, and IgM (data not shown). Serum cytokines before chemotherapy were measured by enzyme-linked immunosorbent assay (ELISA). Interleukin-1β, -2, -3, -4, -7, and -8, granulocyte macrophage-colony stimulating factor (GM-CSF), and stem-cell factor were below the lower limits of examination. Serum tumor necrosis factor-α (TNF-α) and IL-6 were 62 and 16 pg/ml, respectively. The minimum concentrations of TNF-α and IL-6 which could be determined by our ELISA were 5 pg/ml and 3 pg/ml, respectively. These cytokines were not detectable in sera from healthy individuals (data not shown). Macrophage-colony stimulating factor (M-CSF) was 2,003 U/ml. By surveillance of circulating M-CSF concentration in 634 normal subjects using our ELISA system (Midori Juji Co., Ltd., Tokyo, Japan), normal serum M-CSF concentration was evaluated to be 756 ± 147 U/ml. Accordingly, serum M-CSF concentration in this patient was about three times higher than in normal controls. Serum total cholesterol level was 109 mg/dl, which was below normal.

Because of severe dyspnea and hypoxia, treatment with 30 mg doxorubicin, 400 mg cyclophosphamide (CPA), and 1 mg vincristine (VCR) for a day combined with 500 mg/day of methylprednisolone for 3 days was begun immediately after biopsy. A week after the initial therapy, the same doses of CPA and VCR were given and oral prednisolone (PSL) was begun at 40 mg/day. Systemic lymphadenopathy disappeared within a week, and abnormal laboratory test results became normal. Serum M-CSF level fell to 1,076 U/ml a month after therapy was instituted. Interstitial shadow and pulmonary functions became normal after chemotherapy. Total serum cholesterol rose to 224 mg/dl 6 weeks after starting chemotherapy. The dose of PSL was tapered to 5 mg/day, and the patient is alive and well as of October 1996.

DISCUSSION

We describe a case of MCD whose serum M-CSF concentration was elevated and, after chemotherapy, reduced. It has been reported that there are differences between CD and MCD with regard to prognosis, including a risk of developing other malignancies, ages of the affected, and laboratory findings [5,9]. Although the importance of IL-6 in both CD and MCD is now widely accepted, there seems to be a difference between CD and MCD regarding cellular origin of IL-6 [6–8]. Recently, Ishiyama et al. [8] reported that in MCD, the cells which express IL-6 mRNA in lymph nodes and produce IL-6 in peripheral blood are monocyte/macrophage cells but not plasma cells, as shown by in situ hybridization and immunohistochemistry. However, Yoshizaki et al. [6], using immunocytochemistry, reported that blastoid B cells in the germinal center of the enlarged lymph node produce IL-6 in CD. In the present case, not only serum M-CSF but also IL-6 and TNF-α were elevated, which suggests that monocytes/macrophages were activated in this patient.

M-CSF is a cytokine which has multibiological functions, including effects on cholesterol metabolism. Administration of M-CSF to animals has been reported to lower plasma cholesterol levels, and the same observation has been made in patients with chronic neutropenia receiving M-CSF [10,11]. Although a cholesterol-reducing effect by GM-CSF and G-CSF has also been

reported [12,13], it seems unlikely that both cytokines were related to this effect in our patient, because her serum GM-CSF level was below the lower limits of examination and the peripheral leukocyte count was within normal limits. In the present case, the change in total serum cholesterol levels before and after chemotherapy may be explained by the effect of M-CSF. Moreover, Lehnert et al. [14] reported that an increase in the number of alveolar macrophages occurs during pulmonary fibrosis, and that M-CSF and GM-CSF may play important roles in fibrogenetic lung disorders. It was further reported that 25% of patients with MCD also had pulmonary fibrosis confirmed by biopsy or autopsy [15]. In the present case, interstitial shadow and constrictive pulmonary dysfunction at presentation might be related to the effects of M-CSF.

The mechanisms of the elevated serum concentration of M-CSF in MCD are uncertain. However, there have been several reports which may support the possible involvement of M-CSF in MCD. It was reported that IL-6 and TNF-α were significantly expressed in monocytes after activation by M-CSF in vitro [16,17]. Therefore, M-CSF may indirectly take part in the pathogenesis of MCD by stimulating IL-6-producing cells. It may be necessary to pay attention to the function of monocytes and macrophages as well as to B-cell function in order to understand the pathophysiology of MCD.

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